

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re the application of:

EGGEN, et al.

Serial Number: Unknown

Group: 1639 (anticipated)

Filed: This date

Examiner: Examiner Baker (anticipated)

For: Process for rapid solution synthesis of peptides

**Petition to Make Special Pursuant to 37 CFR §1.102**

Honorable Commissioner of Patents  
Washington, D.C. 20231

Sir:

Applicants respectfully file this Petition to Make Special pursuant to 37 CFR §1.102.

Please charge any required fees to deposit account 02-2334.

**I. Petition**

Applicants respectfully petition the Commissioner for this application to be considered special and be taken out of turn, for expedited prosecution. The application has not yet been examined. Applicants include the authorization to charge deposit account 02-2334 in the amount prescribed by 37 CFR §1.17(h) as a fee for this petition.

**II. Claims Directed to a Single Invention**

Applicant believes the claims are directed to a single invention. However, if the Examiner decides that a Restriction Requirement is appropriate, please feel free to contact Applicants' attorney, William P. Ramey, III, for an election at (302) 933-4034.

### **III. Statement of Search**

This statement serves as verification that a search was performed in relevant classes related to Combinatorial Chemistry. The patent classes searched included US Classes 549, 558, 530, and 546. As well, the search encompassed non-patent publications. The results of the search are included.

### **IV. Copies**

One copy of each reference is included with this petition with a form 1449.

### **V. Discussion of Cited Art**

#### **A. Statement of Claims of the present Application**

In an embodiment, the invention of the present application is a process for rapid solution synthesis of a peptide in an organic solvent or a mixture of organic solvents, the process comprising repetitive cycles of steps (a)-(d):

(a) a coupling step, using an excess of an activated carboxylic component to acylate an amino component,

(b) a quenching step in which a scavenger is used to remove residual activated carboxylic functions, wherein the scavenger may also be used for deprotection of the growing peptide,

(c) one or more aqueous extractions and

optionally, (d) a separate deprotection step, followed by one or more aqueous extractions, wherein

the process comprises at least one step (b), referred to as step (b'), in which an amine comprising a free anion or a latent anion is used as a scavenger of residual activated carboxylic functions.

The prior art searched does not teach and/or disclose the claims of the present invention.

Applicants were unable to locate any relevant patents. A search of the literature provided the following references:

**B. References**

**a. Carpino et al.**

An article titled "The 1,1-Dioxobenzo[*b*]thiophene-2-ylmethyloxycarbonyl (Bsmoc) Amino Protecting Group," Carpino et al. (J. Org. Chem., 1999, 64, pp. 4324-4338) discloses details for the use Bsmoc amino-protecting group for both solid phase and rapid continuous solution synthesis. (See Exhibit A). This process is known as the Carpino process. The Carpino process scavenges activated carboxylic functions and Bsmoc functions are removed in one and the same step using a polyamine. Applicants' new process is an improvement. Under Applicants' claimed process, deprotection does not necessarily take place under the same reaction conditions as the scavenging of excess activated carboxylic functions. Furthermore, the Carpino process suffers from hydrophobicity problems when removing residual activated carboxylic functions. However, Applicants' invention does not use a polyamine and, consequently, does not suffer from these problems. Applicants' invention leads to hydrophilic scavenged compounds.

**b. Bernard et al.**

An article titled "Peptide Synthesis by Sappho Technology" by Bernard et al. (1996, Industrial Chemistry Library, pp. 405-415) discloses a solution based peptide synthesis process/system. (See Exhibit B). The system comprises an organic solvent, non miscible with

water; a phenolic additive; and, a lipophilic, non-polymeric, aromatic carboxyl protecting group protector. Further, as with the Carpino process, an acid is required to deprotect (dry HCL).

Under Applicants' claimed process, deprotection does not necessarily take place under the same reaction conditions as the scavenging of excess activated carboxylic functions. Furthermore, the Carpino process suffers from hydrophobicity problems when removing residual activated carboxylic functions. However, Applicants' invention does not use a polyamine and, consequently, does not suffer from these problems. Applicants' invention leads to hydrophilic scavenged compounds. As can be seen, Applicants' invention is patentable over the disclosure of Bernard et al.

**c. Sugawara et al.**

An article titled "A solution-phase synthesis of Fragment Peptide Derivatives Using an Automated Synthesis Apparatus," Sugawara et al. (1996, Peptide Chemistry, 33, pp. 57-60) discloses a fully automated synthesis system for preparing and isolating various kinds of pharmaceutical compounds. (See Exhibit C). Particularly, the article discloses a solid phase synthesis and the difficulties with purification. Further, the article discloses solution based automated peptide synthesis. The article only generally discusses peptide synthesis and gives no specifics. Applicants' invention specifically discloses a novel process that does not use a polyamine and, consequently, does not suffer from prior art problems of hydrophobicity. Applicants' invention leads to hydrophilic scavenged compounds. As can be seen, Applicants' invention is patentable over the disclosure of Sugawara et al.

**d. Nozaki et al.**

An article titled "Rapid Peptide Synthesis in Liquid Phase...." Nozaki et al. (Bull. Chem. Soc. JP., 1982 55(7), pp. 2165-68)(hereinafter referred to as the Nokia article) discloses a process for peptide synthesis by the preparation of a protected angiotensin II and a protected delta sleep inducing peptide. (See Exhibit D). The Nozaki article discloses a solution based synthesis route, referred to as the hold in solution method. The article states that a water-based environment can be maintained throughout the process. The process entails the acylation of a benzyl ester of amino acid or peptide; washing of the organic layer; acidolysis of  $\alpha$ -amino protector; neutralization and washing. The Nozaki article does not disclose a process for the preparation of compounds containing one or more amide bonds using an excess of an activated carboxylic component to acylate an amino component, wherein after the acylation an amine comprising a free anion or a latent anion is used as a scavenger the residual activated carboxylic functions. Accordingly, the Nozaki article does not disclose Applicants' invention.

**e. Cheng et al.**

An article titled "Liquid phase parallel synthesis...", by Cheng et al. (Tetrahedron Letters 40, 1999, pp. 8975-8978)(hereinafter referred to as the Cheng article) discloses a process for rapid synthesis of chemical libraries. (See Exhibit E). The Boc-protected iminodiacetic acid template was attached to the hydroxyl end groups of PEG monomethyl ether (MeO-PEG) by reacting MeO-PEG with excess anhydride in the presence of pyridine. The Cheng article does not disclose a process for the preparation of compounds containing one or more amide bonds using an excess of an activated carboxylic component to acylate an amino component, wherein after the acylation an amine comprising a free anion or a latent anion is used as a scavenger the

residual activated carboxylic functions. Accordingly, the Cheng article does not disclose Applicants' invention.

**f. Wallace**

An article titled "Microsystem technology: a powerful tool for biomolecular studies..." by Wallace (1999, *Biomethods*, 10, pp. 225-240)(Exhibit F) discloses a review of various libraries of peptides and combinatorial techniques for their formation. On page 225, the article specifies three types of systems it will investigate, including (1) bacteriophage surface-displayed libraries, (2) support-bound libraries, and (3) non-support-bound libraries. Section 8.3, on page 236, sums up that several microbial EPTase inhibitors have been identified that act as FPP competitors, none of these is peptidic in nature. Accordingly, the article focused primarily on FTPase inhibitors. The article does not disclose a process for the preparation of compounds containing one or more amide bonds using an excess of an activated carboxylic component to acylate an amino component, wherein after the acylation an amine comprising a free anion or a latent anion is used as a scavenger the residual activated carboxylic functions. Accordingly, the '361 patent does not disclose Applicants' invention.

**g. Gravert et al.**

An article titled "Soluble polyethylene glycol supports for..." by Gravert et al. (*Combinatorial Chemistry and Drug Discovery*, 1997, 22(10), pp. 1147-1150)(hereinafter referred to as the Gravert article) discloses a process for the synthesis of small molecule libraries. (See Exhibit G). The process disclosed uses PEG as a soluble support whereby the benefits of both the solid support and the liquid phase may be enjoyed. The Gravert article does not disclose

a process for the preparation of compounds containing one or more amide bonds using an excess of an activated carboxylic component to acylate an amino component, wherein after the acylation an amine comprising a free anion or a latent anion is used as a scavenger the residual activated carboxylic functions. Accordingly, the Gravert article does not disclose Applicants' invention.

**h. US Pat. No. 5,221,754 (the '754 patent)**

The '754 patent discloses 2-propenyl chloroformate compounds and derivatives thereof used in peptide synthesis. (See Exhibit H). The patent specifically discloses Michael addition amine protecting groups. (Col. 1, ll. 55-62). However, a nucleophile is required to remove the protecting group. (See Col. 2, ll. 10-24). The '754 patent does not disclose a process for the preparation of compounds containing one or more amide bonds using an excess of an activated carboxylic component to acylate an amino component, wherein after the acylation an amine comprising a free anion or a latent anion is used as a scavenger the residual activated carboxylic functions. Accordingly, the '754 patent does not disclose Applicants' invention.

**i. US Pat. No. 6,310,180 (the '180 patent)**

The '180 patent discloses a method for peptide synthesis that requires neither protecting groups nor activation of the C- $\alpha$  carboxyl groups. (Exhibit I). A rationale for the process of the '180 patent entails first that unprotected large peptide segments have significant advantages of capably forming ordered structures and conformational assistance. Second, the bond that forms between the two segments is not necessarily between the  $\alpha$ -amine but is rather between the  $\alpha$ -carboxylic acid and the side chain of the  $\alpha$ -amino terminus using an orthoganol coupling method. The '180 patent does not disclose a process for the preparation of compounds containing one or

more amide bonds using an excess of an activated carboxylic component to acylate an amino component, wherein after the acylation an amine comprising a free anion or a latent anion is used as a scavenger the residual activated carboxylic functions. Accordingly, the '180 patent does not disclose Applicants' invention.

**j. US Pat. No. 6,277,958 (the '958 patent)**

The '958 patent discloses a method for producing a pep[tide thiol ester using fluoren-9-ylmethoxycarbonylamino acid (Fmoc-acid). (Exhibit J). The method binds and then removes Fmoc groups to and from the amines. A thiol ester bond is utilized to bind the Fmoc to the amine. The '958 patent does not disclose a process for the preparation of compounds containing one or more amide bonds using an excess of an activated carboxylic component to acylate an amino component, wherein after the acylation an amine comprising a free anion or a latent anion is used as a scavenger the residual activated carboxylic functions. Accordingly, the '958 patent does not disclose Applicants' invention.

**k. US Pat. No. 6,204,361 (the '361 patent)**

The '361 patent discloses a process for forming an N- $\alpha$ -amino protected amino acid fluoride in situ by treating an N- $\alpha$ -amino protected amino acid with an ionic fluoride salt in the presence of a peptide coupling agent. (Exhibit K). In a broad sense, the patent discloses a process for preparing N-protected amino acid fluoride which comprises mixing a N-protected amino acid or acylating derivative thereof with a fluorinating effective amount of an ionic fluoride salt in the presence of a coupling agent under conditions effective to form said protected amino acid fluoride. The '361 patent does not disclose a process for the preparation of

compounds containing one or more amide bonds using an excess of an activated carboxylic component to acylate an amino component, wherein after the acylation an amine comprising a free anion or a latent anion is used as a scavenger the residual activated carboxylic functions. Accordingly, the '361 patent does not disclose Applicants' invention. In fact, Applicants' background section specifically discusses this prior art process and how the claimed invention is different.

**l. US Pat. No. 5,510,491 (the '491 patent)**

The '491 patent discloses reagents for use in the rapid synthesis of peptides. Specific reagents are disclosed. (Exhibit L). The reagents disclosed are not those used by Applicants' invention. Accordingly, the '491 patent does not disclose Applicants' invention.

**m. US Pat. No. 5,101,059 (the '059 patent)**

The '059 patent discloses blocking groups to protect reactive substituents of amino acids and other organic compounds. (Exhibit M). Embodiments of the patent are especially useful in peptide synthesis. Most particularly, the '059 patent's embodiments are useful for synthesizing acid sensitive peptides. The blocking groups of Applicants' invention are not the same. Applicants' invention can be performed in a hydrophilic environment, thereby obviating many of the problems of this prior art patent. Moreover, the '059 patent does not disclose a process for the preparation of compounds containing one or more amide bonds using an excess of an activated carboxylic component to acylate an amino component, wherein after the acylation an amine comprising a free anion or a latent anion is used as a scavenger the residual activated carboxylic functions. Accordingly, the '059 patent does not disclose Applicants' invention.

**n. Liquid-Phase Method for Peptide Synthesis**

Chapter 2 of *Peptides*, Volume 2, “The Liquid-Phase Method for Peptide Synthesis,” Mutter et. al. 1979, discloses various methods employed for peptide synthesis, including segment condensation, stepwise synthesis, and solid-phase (Merrifield), liquid-solid-phase techniques, and liquid phase techniques utilizing polyethylene glycol as a support.

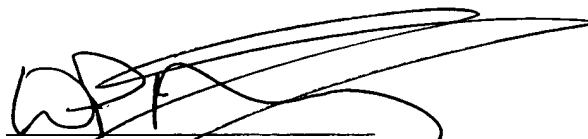
Applicants’ new process is an improvement. Under Applicants’ claimed process, deprotection does not necessarily take place under the same reaction conditions as the scavenging of excess activated carboxylic functions. Further, Applicants’ invention does not use a polyamine and, consequently, does not suffer from hydrophobicity problems. Applicants’ invention leads to hydrophilic scavenged compounds. Therefore, Applicants’ process is different than those disclosed in this art.

**VI. Conclusion**

Applicants have complied with 37 CFR §1.102 in requesting special status be granted to this application. As can be seen, the prior art does not disclose Applicants’ invention. Accordingly, Applicants respectfully request expedited prosecution and allowance of the claims to issue. Please charge any required fees to deposit account 02-2334. Further, Applicants respectfully request that the Examiner contact Applicants undersigned attorney for an interview to facilitate allowance of the case.

Attorney Docket Number O 2000.662 US D1

Respectfully submitted,

A handwritten signature in black ink, appearing to be 'WPR', written over a horizontal line.

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